

I. 35 U.S.C. § 103(a) over Chen, Bianchi, O’Leary and Benedict

Claims 1-19 and 21-27 are rejected under 35 U.S.C. § 103(a) for allegedly being unpatentable over U.S. Pat. 5,707,962 (Chen), in view of U.S. published Application 2001 0018614 (Bianchi), U.S. Pat. 5,405,390 (O’Leary); and U.S. Pat. 6,679,918 (Benedict).

Each of claims 1-19 and 21-27 includes as an element “**an exothermic salt that heats upon contact with a reconstitution fluid.**” [Emphasis added in bold.] The Applicants previously argued that the cited art, alone or in combination, does not teach or suggest a composition having an “exothermic” salt nor any of the species of salts specifically itemized in the specification and in claims 11 and 21 (“**Magnesium chloride, Sodium sulfate, Magnesium sulfate**, or a combination thereof”). [Response to the Official Action of 06/24/05; emphasis added in bold]. In response to this new element, the Patent Office contends that “the prior art suggests adding therapeutically useful agents and does suggest water soluble salts.” [Official Action at page 3.] Then, without any factual support in the record, the Patent Office goes on to state that “[t]he dissolution of a salt in water is typically an exothermic reaction and thus, would appear to be exothermic.” [Official Action at page 2.] Applicants and the art respectfully disagree.

Chen discloses “compositions with enhanced osteogenic potential” [Chen at the Title.] One of the components of the composition is “at least one . . . calcium containing compound.” [Chen at col. 2, lines 34-35; and 57.] According to Chen, “calcium containing compounds” is described “such as **calcium hydroxide, calcium lactate and inorganic or organic calcium salts** may also be sorbed onto the matrix.” Chen does not disclose the generic use of other salts. Moreover, the name “calcium containing compounds” precludes non-calcium salts. The other references do not make up for this deficiency. O’Leary discloses only sodium EDTA (which is a chelating agent) and 1N sodium hydroxide (which is a solution of a base/not a dry exothermic salt). Computer searches of the text of O’Leary establish that O’Leary fails to even mention the terms “calcium” or “magnesium,” and thus, establish that O’Leary fails to disclose any water-soluble magnesium or calcium salts. A computer search of the text of Bianchi establish that Bianchi fails to even mention the terms “sodium,” “calcium” or “magnesium,” and thus, establish that Bianchi fails to disclose any

water-soluble sodium, magnesium or calcium salts. The fourth and final cited reference, Benedict, only mentions “calcium phosphate salt” in relation to its use in a prior art patent [Benedict at col. 1, line 34.] Benedict never mentions the terms “magnesium” or ‘sodium” and thus, could not disclose or suggest any water-soluble magnesium or sodium salt, and particularly not those recited in claims 11 and 21. Thus, of the four cited references, none mentions any of the magnesium or sodium salts recited in claims 11 and 21 of the Applicants’ invention.

Separately, when the word “salt” is searched in the four cited references, Chen mentions “specific inorganic salts.” [Chen at col. 5, line 32.] However, the only “specific inorganic salts” mentioned in Chen are “calcium hydroxide, calcium lactate and inorganic . . . calcium salts” which are “sorbed into the matrix.” [Chen at col. 5, lines 45-47.] In contrast, O’Leary teaches the **removal** of all salts from his composition by dialysis:

The solid form of the osteogenic composition can also be obtained by placing the viscous liquid composition, which has been **titrated** to an **appropriate pH**, in a cellulose dialysis bag, with **the resulting salts removed by dialysis**.

[O’Leary at col. 2, lines 53-57; emphasis added in bold.]

More importantly, the salts referenced in O’Leary were formed in the solution by titration to the “appropriate pH” with an acid or base. Hence, at no time, does O’Leary teach or suggest a solid composition having an “exothermic salt.” As mentioned above, Benedict has a single use of the word “salt”. That reference is only to “calcium phosphate salt” which is used in the description of a prior art reference. [Benedict at col. 1, line 34.] Bianchi, which fails to mention sodium, calcium or magnesium, mentions a single salt, a “zirconium salt,” as a crosslinking agent along with glutaraldehyde. [Bianchi at paragraph 78.] Thus, the cited references, alone or in combination, fail to teach or suggest the use of water-soluble salts in general, and O’Leary specifically **teaches away** from the use of salts by teaching the removal of all salts by dialysis. *See Monarch Knitting v. Sulzer*, 45 USPQ2d 1977, 1984 (Fed. Cir. 1998) (“A prior art reference may be considered to teach away when ‘a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in

the reference, or **would be led in a direction divergent from the path taken by the applicant.**"); emphasis added in bold. For this reason alone, the combination of Chen, Benedict, O'Leary and Bianchi fail to make a prima facie case of obviousness against any of the present claims. *See In re Fine*, 5 USPQ2d 1596, 1599 (Fed. Cir. 1988) ("error to find obviousness where references 'diverge from and teach away from the invention at hand'"); *citing Gore v. Garlock*, 220 USPQ 303, 311 (Fed. Cir. 1983).

A. One Skilled in the art recognizes that the Patent Office's Position that salts are typically exothermic is incorrect and lacks support in the record

In their response to the Official Action of 06/24/05, the Applicants pointed out to the Patent Office that there was no support in any of the cited references for the use of an "exothermic salt":

The cited art, alone or in combination, does not teach or suggest a composition having an "exothermic" salt nor any of the salts specifically itemized in the specification. For these reasons, claims 1-19 would not have been unpatentable over U.S. Pat. 5,707,962 (Chen) or U.S. Pat. 6,180,605, in view of U.S. published Application 2001 0018614 (Bianchi), U.S. Pat. 5,405,390 (O'Leary) and U.S. Pat. 6,679,918 (Benedict).

[Response to the Official Action of 06/24/05 at page 12; emphasis added in bold.]

Due to the lack of factual support in the record, the Patent Office relied upon an "inherency" argument but without citing an outside reference for support:

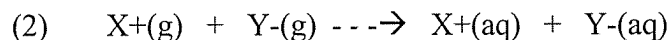
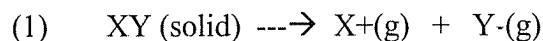
The dissolution of a salt in water is **typically** an exothermic reaction and thus, **would appear to be exothermic.**

[Official Action at page 2: emphasis added in bold.]

However, "inherency" is not relevant in an obviousness rejection. If the Patent Office is relying upon some knowledge in the art, then it **must** produce a reference supporting its allegedly factual position. *See In re Sportmann*, 150 USPQ 449, 452 (CCPA 1966) ("We are

of the opinion that if the Patent Office wishes to reply on what ‘Those familiar with spray drying would know,’ it **must** produce some reference showing what such knowledge consists of.”) However, in the present case, the Patent Office cannot do so because its unsupported position is contrary to the facts and the knowledge in the art.

In particular, the Applicants cite to the Patent Office the following references on salts which disclose that common salts such as sodium chloride, potassium chloride, potassium nitrate, ammonium chloride, ammonium nitrate, ammonium bromide, ammonium thiocyanate are all endothermic – which is totally contrary to the Patent Office’s contention of fact. [See Exhibit A: Ask a Scientist. “Endothermic Reactions”.] The “Ask a Scientist” reference states that not only KCl (potassium chloride) but “pretty much all salts have this [**endothermic**] property. According to the reference, the dissolution of a salt is broken down thermodynamically into the following two steps:



Step (1) is highly **endothermic**; . . . Step (2) is pretty exothermic. . .
.So (1) is more endothermic than (2) is exothermic.

[Exhibit A: Ask a Scientist at page 1; emphasis added in bold.]

Consistent with the general statement in Exhibit A (that upon dissolution in water pretty much all salts are endothermic), the Applicants rely upon Exhibit B: Haig, et al., Journal of Endochemistry, Phys. Dut. Aspects 110, “Endothermic Reactions” Oct 2004. Exhibit B discloses that the dissolution of KNO₃ (page 1), ammonium chloride (page 2), ammonium nitrate (page 2), ammonium bromide (page 2) and ammonium thiocyanate (page 2) are endothermic. In fact, the Table on page 2 of Exhibit B shows that the addition of 0.05 mol of the various ammonium salts to 20 ml of water lowers the temperature of the water by 8.1° C to 13.1° C.

Finally, the Applicants have shown above that the four references cited by the Patent Office do not teach or suggest the general **addition** of dry salts to a reconstitution fluid. In fact, O’Leary teaches the opposite by teaching the **removal** of salts already in the solution by

dialysis. [O’Leary at col. 2, lines 53-57.] However, even if we assume for the sake of argument that the art taught the general addition of salts to the composition, there is no teaching or suggestion in any of the PTO references that the salts would be exothermic salts. Exothermic salts are special and are generally formed from hygroscopic salts that have been heated to drive off the water and render them “anhydrous.” [See e.g., Exhibit C: discussing anhydrous copper sulfate] Such a process requires that energy be put into the system. Such energy and additional processing increases the cost of the “anhydrous” salt. Therefore, it is not logical that one skilled in the art would add a more expensive dehydrated salt to water (rendering it hydrated), when the less expensive hydrated form is available, particularly when the art has not acknowledged or recognized a purpose that would be served by the use of the more expensive anhydrous salt. Moreover, none of the four PTO cited references even mentions the word “exothermic” and thus, none could have suggested the purpose contemplated by the Applicants.

For all these reasons, the combination of Chen, Benedict, O’Leary and Bianchi fails to make a *prima facie* case of obviousness against pending claims 1-19 and 21-27. The allowance of claims 1-19 and 21-27 is respectfully requested.

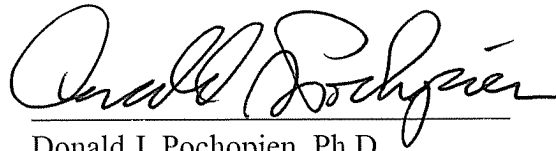
SUMMARY

Claims 1-19 and 21-27 are pending. In view of the arguments and evidence herein, all bases for rejection of claims 1-19 under 35 U.S.C. § 103(a) have been rebutted. For these reasons, claims 1-19 and 21-27 are in condition for allowance

Respectfully submitted,

McANDREWS, HELD & MALLOY, LTD.

By:



Donald J. Pochopien, Ph.D.

Registration No. 32,167

Attorney for Applicants

500 West Madison Street

Suite 3400

Chicago, Illinois 60661

(312) 775-8133

Dated: August 21, 2006

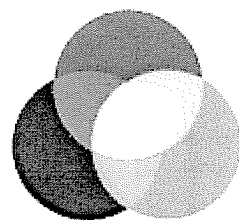
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EXHIBIT A



Ask A Scientist®

Chemistry Archive



NEWTON
Ask A Scientist

Endothermic Reactions

> name Dave
> status student
> age 16

> Question - why does a solution of water and KCl get colder when you add
>the KCl to the water?

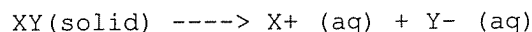
The reaction between water and KCl must be endothermic. In other words, it takes in energy instead of giving off energy.
Van Hoeck

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Hi, nice question.

Pretty much all salts have this property, and (hopefully) the explanation will make it clear why this is.

It is a good approximation in many reactions to equate the heat absorbed/liberated with the net energy change of the reaction. This in turn is often approximately equal to the summed energies of the bonds broken/formed upon proceeding from reactants to products. When a simple XY salt is dissolved, we describe it by the reaction



This can be broken up, at least mentally / thermodynamically, into 2 steps:

- (1) $XY(\text{solid}) \rightarrow X^+(\text{g}) + Y^-(\text{g})$
- (2) $X^+(\text{g}) + Y^-(\text{g}) \rightarrow X^+ (\text{aq}) + Y^- (\text{aq})$

Step (1) is highly endothermic; lots of energy is required to blast a salt into gas-phase ions, because the ion-ion force (Coulomb's Law) is very, very strong compared to all other chemical bonds, and an ionic salt has many ion-ion attraction forces in the crystal. Step (2) is pretty exothermic. Why? Well, bond-breaking is endothermic, so bond-forming must be exothermic. Solvation of ions in water involves the creation of water-ion "bonds" (actually these are ion-dipole electrostatic interactions). But ion-dipole forces are not quite as strong as ion-ion forces. So (1) is more endothermic than (2) is exothermic, and the overall reaction (which is the sum

of 1 and 2) ends up being endothermic.

I hope this helps - best regards.

Prof. Topper
Dept of Chemistry
The Cooper Union
New York, NY

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Argonne National Laboratory, Division of Educational Programs, Harold Myron, Ph.D., Division Director.*

EXHIBIT B

Endothermic reactions

Haig, H.I., Herema, H.R.M. & Baam, B.M.
Vrije Universiteit Amsterdam, The Netherlands

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Summary

This article describes the determination of the highest temperature decrease in dissolving four different ammonium salts. To determine the temperature decrease a coffee-cup calorimeter is used. The dissolution of ammonium nitrate tends to be the most endothermic. From this it is assumed that the magnitude of the lattice energy minus the solvation energy is largest for the tested ammonium nitrate. This leads to further questions: what is the effect in temperature decrease when larger concentrations of ammonium nitrate are used? What is the relation between concentration and temperature decrease? Can a 'cold pack' be designed that has a decrease of exactly 10.0 °C?

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Salts, Endothermic reactions, Sports

Introduction

Some spontaneous chemical processes are endothermic reactions. Here we will consider three types of endothermic processes.

- Phase changes. For example:



- Dissolution processes. For example:



- Chemical reactions that involve the production of new substances such as the reaction between hydrated barium hydroxide and ammonium chloride (1).

A closer look at each of these processes shows that either a gas is formed from solid or liquid reactants, or a solid dissociates in water, forming hydrated ions. All vaporisation processes result in cooling the surroundings of the system (an endothermic process) as heat is absorbed to evaporate the liquid (or solid in the case of sublimation). A few drops of propanone on the skin has a remarkable cooling effect. The temperature decrease, ΔT in Table 1, is related to the amount of liquid that has evaporated and this in turn is related to the vapour pressure of the evaporating liquid.

The vaporisation process of sweating (Fig. 1) keeps us cool. Evaporative cooling is more than a chemical curiosity. Evaporative coolers provide air conditioning in homes and cars. In sports pressurized containers of 1,2-dichloroethene are used as a spray

to break up muscle spasms.

Solvent	ΔT (°C)	$p(10^5 \text{ Pa})$
Propanone	-46.5	3.2
Methanol	-35.6	1.6
Benzene	-22.7	1.3
Ethanol	-21.5	0.78
Water	-6.6	0.32

Table 1: The evaporative cooling effect ΔT and the vapour pressure p at 298.2K for several solvents.



Fig. 1: sweating person

The process of dissolving salts in water results in either an endothermic or exothermic effect.

Dissolution of anhydrous calcium chloride results in a heating effect, whereas dissolution of ammonium salts result in a cooling effect (2). From the known cooling effect of various ammonium salts the question arises: *which in water dissolved ammonium salt results in the highest cooling effect?*

Experimental procedure

Four different ammonium salts are compared: ammonium chloride (NH_4Cl), ammonium nitrate (NH_4NO_3), ammonium bromide (NH_4Br) and ammonium thiocyanate (NH_4SCN).

A coffee-cup calorimeter (Fig. 2) is filled with 20.0 mL distilled water. The temperature is measured and recorded. 0.050 mol of the first ammonium salt is added. The mixture is stirred and after 2 minutes the temperature is measured again and recorded. This experiment is repeated several times. Successively for the other three salts the temperature changes are determined in exactly the same way as for the first salt.

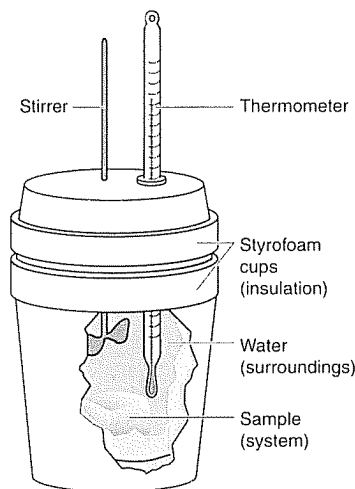


Fig. 2: Experimental set-up: a coffee-cup calorimeter

Data analysis

For each ammonium salt the difference in temperature before and after the salt is added to the water (ΔT) is determined. The various ΔT 's are averaged and the deviations are determined. The average values of each of these measurements are presented graphically.

Results

In all cases the starting temperature of the water in the coffee-cup calorimeter was 24.0 °C. The observed and average temperature changes for each of the four ammonium salts are given in Table 2.

Ammonium salt (0.050 mol)	ΔT averaged (°C)
1. Ammonium chloride	-8.1 ± 0.2
2. Ammonium nitrate	-13.1 ± 0.1
3. Ammonium bromide	-9.2 ± 0.3
4. Ammonium thiocyanate	-10.9 ± 0.2

Table 2: Temperature changes and deviations on dissolution of various ammonium salts (0.050 mol) in water.

The dissolution of all four ammonium salts results in a negative ΔT (Fig.3).

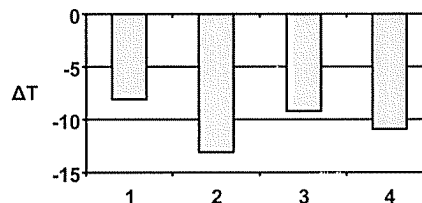


Fig. 3: Temperature change (ΔT in °C) on the dissolution of four different ammonium salts in water.

Conclusion and discussion

From the observed measurements it can be concluded that the dissolution of ammonium nitrate (s) in water results in the highest cooling effect. This finding supports the results found by Letcher & Battino (3).

Dissolution processes, the solute (salt) is dispersed throughout the solvent (water), involve two stages:

- The separation of the ions from one another; and
- The association of separated ions and the water molecules.

Stage (i) is always endothermic and for ionic compounds in water this energy of ionisation is usually very large. Stage (ii) is always exothermic and for ions in water it is called the hydration energy. From the fact that the dissolution of ammonium salts results in a cooling effect, it is concluded that the energy of ionisation in these processes is exceeding the hydration energy. Furthermore from the observed cooling effect of dissolving ammonium nitrate in water it is assumed that for this case the magnitude of the lattice energy (i) minus the solvation (i) energy is largest. Out of this assumption many questions arise: what is the effect in temperature decrease when larger concentrations of ammonium nitrate are used? What is the relation between concentration and change in temperature?

Interestingly, the cooling effect of dissolving ammonium nitrate is used in commercial cold packs. In case of a sports injury the cold pack should not be too cold, because then it causes discomfort; parts of the body can be frostbitten. However, should be cool enough to cool down the injury. So, is it possible to design a cold pack that results exactly in a decrease in temperature (ΔT) of 10.0 °C?

Bibliography

- Kaufman, G.B. & Ferguson, C.A. (1988). The endothermic dissolution of ammonium nitrate. *Journal of Chemical Education*, 65, 2, 267.
- Letcher T.M. & Battino. R. (2001). An introduction to the understanding of solubility. *Journal of Chemical Education*, 78, 1, 103-111.
- Letcher T.M. & Battino. R. (2004). Demonstrating endothermic reactions. *Education in Chemistry*. 7, 105.

EXHIBIT C

Rates of Reaction

Energy - Examples of Endothermic and Exothermic Reactions.

Most reactions are exothermic.

Examples are

- 1) Combustion of methane (natural gas).
- 2) Neutralisation of dilute hydrochloric acid and dilute sodium hydroxide.
- 3) Adding concentrated sulphuric acid to water is highly exothermic (gives out a lot of heat).
- 4) Adding water to anhydrous copper(II) sulphate is exothermic.
Anhydrous copper(II) sulphate is white.
Anhydrous is pronounced "an-high-drus"
Anhydrous means "without water".

Anhydrous copper(II) sulphate is copper(II) sulphate which is completely dry.

When water is added to it, it turns into the familiar hydrated blue crystals.

Hydrated is pronounced "high-dray-tid", it means 'with water'.

This is used as a test for water.

If blue (hydrated) copper(II) sulphate crystals are heated, an endothermic reaction occurs, they lose their water, turn white and become anhydrous copper(II) sulphate crystals again.

The reaction is reversible.

Blue copper(II) sulphate crystals will also turn white in the presence of concentrated sulphuric acid.

Few reactions are endothermic.

Examples are

1) Photosynthesis.

Chlorophyll is a very clever catalyst,
which allows plants to make sugar from carbon dioxide in the air.
The energy needed for the reaction comes from sunlight.

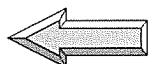
2) The reaction of ethanoic acid with sodium carbonate.

3) Dissolving some salts in water is an endothermic process.

Potassium chloride and ammonium nitrate
both take in energy when they dissolve.

If you put a thermometer in the solution as they are dissolving,
you will see that the temperature drops.

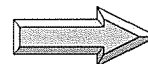
4) Melting, boiling and evaporation
are all endothermic processes (not reactions).



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